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EXAMINER

LUKTON, DAVID

ART UNIT PAPER NUMBER

1653

DATE MAILED: 12 03 2002

22

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/508,635

Applicant(s)

Ballevre

Examiner

David Lukton

Art Unit

1653



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on Sep 25, 2002
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 30, 32-35, and 37-41 is/are pending in the application.
- 4a) Of the above, claim(s) 33 and 34 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 30, 32, 35, and 37-41 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claims \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some\* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s).
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 3 6) ☐ Other:

Pursuant to the directives of paper No. 19 (filed 7/30/02), claim 30 has been amended and claims 31 and 36 cancelled. Claims 30, 32-35 and 37-41 are now pending.

In response to the "election of species" requirement, applicants have elected small intestines as the organ.

Applicants arguments filed 4/15/02 (paper No. 17) have been considered and found persuasive in part.

Pursuant to the election (small intestines), claims 33-34 are withdrawn from consideration. Claims 30, 32, 35 and 37-41 are examined in this Office action.

※

The following is a quotation of the first paragraph of 35 U.S.C. §112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 30, 32, 35 and 37-41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification fails to teach a skilled physiologist how to use protein hydrolyzates and amino acids to promote "recovery" of an organ. As stated in *Ex parte Forman* (230 USPQ

546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988), the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims.

As for the "nature of the invention", it is asserted in the specification (page 8, line 17+) that the disclosed protein hydrolyzates can be used to repair damage to the intestine. Also asserted (page 8, line 20+) is that the disclosed protein hydrolyzates can be used to treat Crohn's disease, diarrhea, colitis or sepsis, and further, that the disclosed protein hydrolyzates can be used to reverse damage to gut epithelial tissue that has resulted from a surgical procedure, or from any other cause. Though not specifically stated, the implication is that various diseases such as hepatitis, cirrhosis of the liver, and kidney infection can be successfully treated. Such diseases cause damage to organ tissue, and if the claimed method is to be effective, the protein hydrolyzates must be effective not only to accelerate wound healing, but overcome the pathological basis of the organ damage.

As for the "working examples", applicants have obtained results which are consistent with the conclusion that if one administers a mixture of all 20 genetically encoded amino acids to a mammal, the relative weights of the stomach, intestine, duodenum jejunum, liver, gastrocnemius, soleus, and extensor will vary slightly if the ratio of amino acids is altered.

This assertion is somewhat suspect, since no statistical analysis has been presented. For example, in the case of the duodenum, the standard deviation would not have to be high at all in order to justify the conclusion that the results are not statistically significant. Without further information as to the variability in the data (that is presented on page 17), it is not particularly meaningful. The results are also not meaningful, since the amount of lipids and minerals (see page 14) were varied simultaneously with the amino acid composition. Furthermore, the total amount of amino acids varies from feed mixture to the next. Thus, even if it turns out that the results on page 17 are statistically significant, it has not been determined the extent to which, or even whether, the observed changes in organ weights were the result of varying the amino acid composition, rather than the lipids and minerals. Or maybe the changes in organ weights were due to changes in the total amount of amino acids administered, rather than variations in the amino acid content. Or maybe the changes in organ weights were due to changes in differential metabolism of the peptide fragments which were produced by the different hydrolysis methods (hydrolyzate 1, hydrolyzate 2 or hydrolyzate 3). Thus, applicants have varied several different variables simultaneously, and it is impossible to determine the effects of any one of them taken alone. Furthermore, there is no control experiment. What are the results supposed to be relative to? If the feed compositions (feed 1 - feed 5) were given to rats which were already exhibiting a positive nitrogen balance, would there be any effect at all of the different feeds? Even if

it turns out that the results on page 17 are statistically significant, and if could be determined what the cause (among the numerous variables) of the variance in organ weights might be, the results are still not meaningful with respect to the claimed invention. The claimed invention is not drawn to a method of randomly altering the weights of selected organs. And even if the claims were drawn e.g., to a method of increasing the weight of the stomach, it is not at all clear how one would proceed. It may be true that if one uses, e.g., feed #5 rather than feed #1, one will obtain a slightly higher weight of the stomach. If it were to turn out that this difference is due to the amino acid content, rather than to the lipids and minerals (or one of the other variables), how would one translate the results of feed #5 *versus* feed #1 into a general method of increasing stomach weight? Which amino acids are necessary, which are sufficient? What degree of hydrolysis will produce the intended results, and which will not? And even if enablement existed for a method of increasing the weight of specific organs (a point which is not conceded), how would that translate into a showing of enablement for the claimed invention, which is that of using protein hydrolyzates and amino acids to promote "recovery" of an organ?

The results of a second experiment are presented on pages 21-24. What is shown here is that the rate of protein synthesis varies somewhat depending on which of the five feeds is used. The criticisms of the experimental results on page 17 apply here as well. First, the results are not statistically significant in the absence of further information as to the

variability that is observed from one experiment to the next (for a given feed composition).

Second, there are several different variables (with respect to the feed composition itself) which are altered simultaneously. And third, even if applicants were to make a clear assertion as to the specific variable that is supposed to correlate with the increased protein synthesis, and even if there were an experimental basis for such an assertion, this would have little relevance to the claimed invention, which is that of using protein hydrolyzates and amino acids to promote "recovery" of an organ. Applicants have presented no evidence that any such correlation exists between rate of protein synthesis, and recovery of an organ from wounding, physical trauma, or damage from an inflammatory condition. The reality is that one cannot "predict" such "recovery" based on rates of protein synthesis.

The following references discusses the issue of statistical analysis, and more importantly the issue of artifacts or invalid conclusions that can be drawn from an inadequate experimental design, or flawed assumption:

Ludbrook (*Clinical and Experimental Pharmacology and Physiology* 28 (5-6) 488-92, 2001)

Bryant (*Pediatric Allergy and Immunology* 9 (3) 108-15, 1998)

Bezeau (*Journal of Clinical and Experimental Neuropsychology* 23 (3) 399-406, 2001)

Bolton (*Journal of Clinical Pharmacology* 38 (5) 408-12, 1998)

Willenheimer (*Progress in Cardiovascular Diseases* 44 (3) 155-67, 2001)

Chung (*Plastic and Reconstructive Surgery* 109 (1) 1-6, 2002)

Atkinson (*Chronobiology International* 18 (6) 1041-53, 2001).

There are principally two issues with regard to enablement. First, what conclusions can be drawn directly from the results presented on pages 17 and 21-24...? Second, to what extent to those conclusions form the basis for extrapolating to the various inventions that are encompassed? (e.g., repairing of damage to the intestines, treatment of Crohn's disease, diarrhea, colitis or sepsis, hepatitis, cirrhosis of the liver, and kidney infection, reversal of damage to gut epithelial tissue). As a first step in the discussion, it would be helpful if applicants would explain exactly what conclusion they believe can be drawn directly from the results presented on pages 17 and 21-24. Regardless of what conclusion may be drawn directly from the data, the fact is that increasing DNA synthesis or even increasing organ weight does not engender a method of promoting wound healing, or of successfully treating a patient whose organs have been damaged by disease, surgery or trauma. "Undue experimentation" would be required to practice the claimed invention.

\*

Claims 30, 32, 35 and 37-41 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- The claims are drawn to a method of promoting "recovery" of an organ. From what is the organ recovering? Is it a wound, physical trauma, or a disease?
- Claim 30 recites the following:

"...selecting a dietary protein selected from ... a protein hydrolysate... [and]...amino acids..."

Thus, applicants are equating a protein with a protein hydrolysate. If one starts with a large protein (e.g., 50 kD) and enzymatically or chemically cleaves off a small portion (e.g., 10 kD), the result will be a molecule which is both a protein, and a hydrolysate. Thus, it is possible for a protein to be a "hydrolyzed protein", although attempting to equate the two without explanation tends to generate confusion. But it appears that the term "protein hydrolysate" is used and described in the specification to convey a mixture of a significant number of peptides that could be obtained by enzymatic or chemical hydrolysis of a protein. For this embodiment at least, a "protein hydrolysate" is not a protein. And clearly, by any semantic analysis, an amino acid is not a protein. One option would be to create two independent claims, one for protein hydrolyzates, and one for amino acids.

- Each of claims 32 and 34 make reference to the term "degree of hydrolysis". This term is ambiguous. Suppose that one begins with a protein that consists of 100 amino acids. For the sake of simplicity, suppose that the "protein" is really a homopolymer of amino acids (e.g., glutamic acid or arginine); in this way, the molecular weights of all amino acids are the same, which simplifies the analysis. A "degree of hydrolysis" of 30% could be interpreted to mean (for this simple example) that after hydrolysis, there are 70 amino acids which are bonded to at least one other amino acid in peptide linkage, and that there are 30 "free" amino acids. But there are other interpretations. One is that 30% of the initial peptide linkages (of which there are 99) are cleaved by an enzyme or chemical agent, or in other words, there would be about 30 sites of cleavage in this example. In this latter interpretation, there would not necessarily be any "free amino acids". On the other hand, one could "liberate" 30 amino acids (of the initial 100) using an exopeptidase (N-terminal or C-terminal) which would result in a single peptide consisting of 70 amino acids, together with amino acids, such that the weight ratio is about 70:30 (for simplicity, the change in molecular weight resulting from addition of H<sub>2</sub>O to each free amino has not been considered). Thus, what exactly is meant by the term "degree of hydrolysis"...

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The following is a quotation of 35 USC §103 which forms the basis for all obviousness rejections set forth in the Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 30, 32, 35 and 37-41 are rejected under 35 U.S.C. §103 as being unpatentable over Ballard (USP 5,679,771) in view of Duguay (*Journal of Biological Chemistry* **270** (29) 17566-74, 1995).

As indicated previously, Ballard discloses that IGF-1 increases the weight of the gut (including intestines and jejunum) and improves gut function, and accelerates healing of damaged gut tissue. Ballard does not disclose that IGF-1 is a "protein hydrolyzate". Duguay discloses that IGF-1 is produced by enzymatic cleavage of a precursor peptide. Thus, IGF-1 is a "protein hydrolyzate". Duguay does not disclose a method of promoting

recovery of intestines.

When the claims were previously rejected over Ballard taken by itself, applicants argued that Ballard does not disclose that IGF-1 is a protein hydrolyzate. As is now evident, IGF-1 is actually a "protein hydrolyzate". It is probably the case that if one placed pro-IGF-1 in boiling 6 N HCl, one would not obtain IGF-1. However, the claims only require that the given peptide in question could have been produced by hydrolysis of a larger peptide, whether that hydrolysis is catalyzed by an enzyme, or whether the hydrolysis is undertaken chemically.

Thus, the claims are rendered obvious.

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Claims 30, 32, 35 and 37, 38, 40, 41 are rejected under 35 U.S.C. §103 as being unpatentable over Ballard (USP 5,679,771) in view of Wunderlich (USP 5,614,219).

As indicated previously, Ballard discloses that IGF-1 increases the weight of the gut (including intestines and jejunum) and improves gut function, and accelerates healing of damaged gut tissue. Ballard does not disclose that IGF-1 is a "protein hydrolyzate". Nor does Ballard suggest combining the IGF-1 with a protein hydrolyzate prior to administration. Wunderlich discloses pharmaceutical formulations that contain peptides or proteins in combination with gelatin. Wunderlich does not teach a method for promoting recovery of an organ.

The first point to be made is that Wunderlich provides motivation to combine the IGF-1 with gelatin prior to administration. As it happens, gelatin is hydrolyzed collagen. Thus, the two references combined provide motivation to administer IGF-1 in combination with hydrolyzed collagen.

The instant claims are drawn to a method of promoting recovery of an organ (such as the large or small intestine) by a process that comprises administration of a hydrolyzed protein. As such, the claims do not preclude the possibility of also administering an agent in addition to the hydrolyzed protein. This ground of rejection is directed to such an embodiment. The medical practitioner of ordinary skill, in practicing the invention of Ballard and Wunderlich, would be administering protein hydrolyzates in combination with another agent with the expectation that healing of damaged gut tissue will be achieved. The fact that it is the IGF-1, rather than the protein hydrolyzate, that is the active agent does not negate the validity of this rejection.

With respect to claim 37, the argument is that the medical practitioner would not withhold treatment merely because the patient is afflicted with another disorder; claim 37 does not require that the state of muscular atrophy be mitigated by the treatment.

Thus, the claims are rendered obvious.

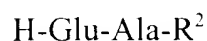
✱

Claims 30, 32, 35 and 37-41 are rejected under 35 U.S.C. §103 as being unpatentable over

Mukai, Kiyoshi (English Abstract of JP-3264525).

Mukai discloses that glutamic acid-containing dipeptides (Glu-Ala, Gly-Gln, Glu-Gly) is effective to prevent catabolism of muscular proteins, and to accelerate synthesis of tissue proteins. Mukai does not disclose that the dipeptides are "protein hydrolyzates". Mukai also does not disclose that "muscular proteins" are organs.

As for the first point, the fact is that the dipeptides contained in the reference could be obtained by enzymatic or chemical hydrolysis of larger peptides. Letting "R<sup>1</sup>" and "R<sup>2</sup>" represent the remainder of the peptide, these larger peptides can be represented as follows (for the case of Glu-Ala):



Thus, if one were to take the first of these two peptides, and treat it with an N-terminal exopeptidase, amino acids would be cleaved off one by one until the C-terminal dipeptide remained. Some purification would probably be necessary, but that would not detract from the fact that the dipeptide had acquired the status of being a "protein hydrolyzate". Similarly, if the second of the two peptides were treated with a C-terminal exopeptidase, amino acids would be cleaved off one by one until the N-terminal dipeptide remained. As for chemical cleavage, various controlled methods of cleaving off amino acids one by one are known to peptide biochemists. Perhaps the best known is the Edman degradation,

which results in cleavage of N-terminal amino acids by reaction of phenylisothiocyanate with the N-terminal amino group, forming a phenylthiohydantoin, and the original peptide (minus the N-terminal amino acid). The claims are not drawn to a method of hydrolyzing proteins, nor are the claims drawn to a two step method in which the first step is protein hydrolysis, and the second step administration to a patient. The reality is that any peptide that one can prepare or isolate or draw the sequence of on paper is indistinguishable from a peptide which has been obtained by hydrolysis of a larger peptide and containing that subsequence.

The second apparent "deficiency" of Mukai is that it does not <sup>teach</sup> that "muscular proteins" are organs. However, this is disclosed, or at least implied in applicants specification. If one compares original claim 7 with original claim 1, it is apparent that applicants are asserting that muscles are organs. This is not consistent with the accepted meaning of the term "organ" (although the heart is certainly an organ, and is composed largely of muscle), but since applicants have asserted that the term "organ", as used in the claims, encompasses muscle, this ground of rejection is applicable.

Thus, the claims are rendered obvious.

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Claims 30, 32, 35 and 37-41 are rejected under 35 U.S.C. §103 as being unpatentable over Mukai, Kiyoshi (JP-3264525).

Mukai discloses (table 8, col 29) that if the nutritional formula of example 3 were

administered to rats, the result was an increase in the weight of the protein of the jejunum, and an increase in the jejunal mucous DNA. The nutritional formula of example 3 contains amino acids and a glutamine dipeptide. Also asserted in the reference is that the disclosed nutritional formula can be used for maintenance of organs and intestinal function.

Thus, given the observed increase in the weight of the jejunum and increased protein synthesis, it would have been obvious to one of ordinary skill that "promotion" of recovery of an organ can be achieved.

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Claim 30 is rejected under 35 U.S.C. §103 as being unpatentable over Goldberg M. (*Horm Metab Res* **12** (3), 94-96, 1980).

Goldberg discloses that administration of a protein hydrolyzate to rats resulted in an increase in DNA synthesis in liver cells. Goldberg does not disclose that the protein hydrolyzate will "promote recovery" of the intact liver. However, one of ordinary skill would have reasoned that if DNA synthesis in liver cells can be increased, damaged liver tissue would heal more rapidly as a result.

Thus, the claim is rendered obvious.

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Claim 30 is rejected under 35 U.S.C. §103 as being unpatentable over Mawatari (USP 5,580,903).

Mawatari discloses that the amino acids alanine and glutamine are effective to regenerate liver. Mawatari does not employ the phrase "promoting recovery" of the liver, but one of ordinary skill would recognize that there is overlap between the phenomenon of regenerating liver, and promoting recovery of liver.

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Claim 30 is rejected under 35 U.S.C. §103 as being unpatentable over Henningfield (USP 5,221,668).

Henningfield discloses (col 10, line 43+) that arginine promotes wound healing. It is apparent from a reading of the instant specification that an acceleration of wound healing is encompassed by the phrase "promoting recovery". Thus, one of ordinary skill would have expected that arginine would promote wound healing in organs and tissues which have been subject to trauma or surgical incision.

Thus, the claim is rendered obvious.

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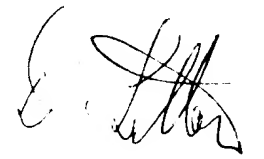
- Reference "AS" (PCT search report) was stricken from the IDS. Sufficient information should be provided so that after issuance of the patent, others may find the references which have been cited.
- Reference "AM" (EP 0,322,589) was stricken from the IDS because of the absence of a translation.
- Reference "AK" was stricken from the IDS because of the absence of a translation.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

  
DAVID LUKTON  
PATENT EXAMINER  
OCT 16 1999